WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Terms	Documents
5780237.pn.	1

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: Refine Search

Recall Text | Clear

Search History

DATE: Friday, October 25, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB; PLUR=YES; OP=ADJ			
L10	5780237.pn.	1	L10
L9	leukotoxin diol	3	L9
L8	L1 and leukotoxin	2	L8
L7	L1 and linoleic acid diol?	0	L7
L6	L3 and diol	59	L6
L5	L3 and (linoleic or leukotoxin)diol	0	L5
L4	L3 and (linoleic or leukotoxin)	23	L4
L3	L2 and (competitive or noncompetitive)	1559	L3
L2	L1 and (ELISA or immunoassay)	3414	L2
L1	((435/7.1)!.CCLS.)	5153	L1

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Search Results -

Terms	Documents
L6 and diagnos?	68

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L7

Refine Search

Recall Text | Clear

Search History

DATE: Friday, October 25, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ			
L7	L6 and diagnos?	68	L7
L6	L3 and human	438	L6
L5	L3 and (blood or urine)	415	L5
L4	L3 and (pre-eclampsia or eclampsia or pregnancy-induced)	2	L4
L3	L2 and (immunoassay or ELISA)	580	L3
L2	L1 and (linoleic acid diol) or glucuronid? or leukotoxin?	1910	L2
L1	hypertension or ARDS or (adult respiratory distress) or cardio? or (lipid metabolism defect)	41294	L1

END OF SEARCH HISTORY

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Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Terms	Documents
L16 and hypertension	1

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L17

Refine Search

Recall Text | Clear

Search History

DATE: Friday, October 25, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB; PLUR=YES; OP=ADJ			
L17	L16 and hypertension	1	L17
L16	L15 and lino? or leukotoxin?	41	L16
L15	hammock.au. or hammock.in.	44	L15
L14	linoleic acid diol and hypertension	0	L14
DB=USPT; PLUR=YES; OP=ADJ			
L13	linoleic acid diol and hypertension	0	L13
L12	linoleic acid diol and pregnancy	0	L12
L11	L10 and pregnancy	19	L11
L10	linoleic acid diol or glucuronide?	290	L10
L9	L4 and (leukotoxin? or linoleic acid diol)	0	L9
L8	L5 and linoleic acid diol	0	L8
L7	L5 and leukotoxin?	0	L7
L6	L5 and (leukotoxin? or linoleic acid diol)	0	L6
L5	L4 and immunoassay	52	L5
L4	eclampsia or (pregnancy induced hypertension)	302	L4
L3	6150415.pn.	1	L3
L2	5780237.pn. or 5955496.pn.	2	L2
L1	4366241.pn. or 4376110.pn. or 4517288.pn. or 4837168.pn.	4	L1

END OF SEARCH HISTORY

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FILE 'HOME' ENTERED AT 14:16:02 ON 25 OCT 2002

=> file caplus

=> d l25 ibib abs 1-13

L25 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:641106 CAPLUS
TITLE: Development of an enzyme immunoassay for linoleic acid diols in urine
AUTHOR(S): Zurek, Gabriela; Gee, Shirley J.; Hammock, Bruce D.
CORPORATE SOURCE: Cancer Research Center, Department of Entomology, University of California, Davis, CA, 95616, USA
SOURCE: Analytica Chimica Acta (2002), 466(2), 247-256
CODEN: ACACAM; ISSN: 0003-2670
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An ELISA for the diol derivs. of linoleic acid, cis-9,10-dihydroxyoctadec-12(Z)-enoic acid (***leukotoxindiol*** , LTXD) and cis-12,13-dihydroxyoctadec-9-(Z)-enoic acid (iso- ***leukotoxindiol*** , iso-LTXD), was developed. Polyclonal antibodies were generated in rabbits using an isomeric LTXD and iso-LTXD mixt. conjugated with keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA). Coating antigens were synthesized by conjugation of LTXD/iso-LTXD, dihydroxystearic acid, ricinoleic acid (OLE), ricelaidic acid (ELA) or 12-hydroxystearic acid to BSA or ovalbumin (OVA). Various linoleic acid derivs. did not cross react significantly. Using the ovalbumin conjugate of ricinoleic acid as a coating antigen, the assay yielded an IC50 value of 8 .mu.g/l LTXD/iso-LTXD and was applied to the anal. of urine samples. Urine samples were treated with glucuronidase to release LTXD/iso-LTXD from its glucuronic acid conjugate. An increase of the LTXD/iso-LTXD signal was clearly obsd. after glucuronidase incubation. Recent evidence suggests that these diols may be involved in diseases such as acute respiratory distress syndrome and cardiovascular diseases, thus this assay will be important in assessing the significance of these compds. as biomarkers for these disease states.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:863088 CAPLUS
DOCUMENT NUMBER: 136:116492
TITLE: ***Leukotoxin*** - ***Diol*** . A putative toxic mediator involved in acute respiratory distress syndrome
AUTHOR(S): Zheng, Jiang; Plopper, Charles G.; Lakritz, Jeffery; Storms, David H.; Hammock, Bruce D.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, School of Pharmacy, Bouve College of Health Sciences, Northeastern University, Boston, MA, 02115, USA
SOURCE: American Journal of Respiratory Cell and Molecular Biology (2001), 25(4), 434-438
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Thoracic Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leukotoxin is clin. assocd. with acute respiratory distress syndrome (ARDS). Recently, we found that ***leukotoxin*** - ***diol*** , the hydrated product of leukotoxin, is more toxic than the parent leukotoxin in vitro. To test if this difference in the toxicity of leukotoxin and ***leukotoxin*** - ***diol*** exists in vivo, Swiss Webster mice were administered leukotoxin or ***leukotoxin*** - ***diol*** . All mice treated with ***leukotoxin*** - ***diol*** died of ARDS-like respiratory distress, whereas the animals exposed to leukotoxin at the same dose survived. Histopathol. evaluation of the lungs revealed massive alveolar edema and hemorrhage with interstitial edema around blood vessels in the lungs of mice treated with ***leukotoxin*** - ***diol*** , whereas the lungs of mice treated with identical doses of leukotoxin had perivascular edema only and little change in alveolar spaces. Immunohistochem. showed that the sol. epoxide hydrolase responsible for the hydrolysis of leukotoxin to its diol is concd. in the vascular smooth

muscle of small and medium-sized pulmonary vessels. In addn., 4-phenylchalcone oxide, an inhibitor of sol. epoxide hydrolase, was found to decrease the mortality induced by leukotoxin but had no effect on mortality induced by ***leukotoxin*** - ***diol*** . These studies provide strong in vivo evidence that leukotoxin may act as a protoxicant and that the corresponding diol is a putative toxic mediator involved in the development of ARDS.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:539978 CAPLUS
DOCUMENT NUMBER: 135:148461
TITLE: Cellular Characterization of ***Leukotoxin*** ***Diol*** -Induced Mitochondrial Dysfunction
AUTHOR(S): Sisemore, Marlene F.; Zheng, Jiang; Yang, Joy C.; Thompson, David A.; Plopper, Charles G.; Cortopassi, Gino A.; Hammock, Bruce D.
CORPORATE SOURCE: Department of Entomology, University of California, Davis, CA, 95616, USA
SOURCE: Archives of Biochemistry and Biophysics (2001), 392(1), 32-37
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leukotoxin, a cytochrome P 450-derived epoxide of linoleic acid, has been implicated as a causative factor in acute respiratory distress syndrome. Conversion of this fatty acid epoxide to ***leukotoxin*** ***diol*** by epoxide hydrolase has been hypothesized as the crit. activation step in leukotoxin-induced cellular toxicity. In both human and insect cells, we obsd. that ***leukotoxin*** ***diol*** causes acute cellular toxicity and that cyclosporin A, an inhibitor of the mitochondrial permeability transition, ameliorates ***leukotoxin*** ***diol*** -assocd. toxicity. To evaluate mitochondria as a target of ***leukotoxin*** ***diol*** , multiple aspects of mitochondrial integrity were evaluated in both cell- and organelle-based assays. ***Leukotoxin*** ***diol*** specifically activated the mitochondrial permeability transition, resulting in release of cytochrome c and subsequent cell death. Pretreatment with cyclosporin A inhibited these effects and, furthermore, limited in vivo toxicity. While the mechanisms underlying leukotoxin-mediated toxicity remain to be fully elucidated, the observation that ***leukotoxin*** ***diol*** disrupts mitochondrial function specifically through activation of the mitochondrial permeability transition suggests at least one mechanism through which ***leukotoxin*** ***diol*** may exert its activity in physiol. contexts. (c) 2001 Academic Press.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:806272 CAPLUS
DOCUMENT NUMBER: 134:173927
TITLE: Toxicity of linoleic acid metabolites
AUTHOR(S): Greene, Jessica F.; Hammock, Bruce D.
CORPORATE SOURCE: Departments of Entomology and Environmental Toxicology, University of California at Davis, Davis, CA, 95616, USA
SOURCE: Advances in Experimental Medicine and Biology (1999), 469(Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury, 4), 471-477
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 22 refs. on the formation of linoleic acid metabolites, synthesis of leukotoxin and isoleukotoxin, toxicity of leukotoxin and isoleukotoxin, and metabolite toxicity (***leukotoxin*** ***diol*** and isoleukotoxin diol).
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:259098 CAPLUS
DOCUMENT NUMBER: 133:69968
TITLE: Metabolism of Monoepoxides of Methyl Linoleate:

Bioactivation and Detoxification
AUTHOR(S): Greene, Jessica F.; Williamson, Kristin C.; Newman, John W.; Morisseau, Christophe; Hammock, Bruce D.
CORPORATE SOURCE: Department of Entomology, University of California at Davis, Davis, CA, 95616, USA
SOURCE: Archives of Biochemistry and Biophysics (2000), 376(2), 420-432
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leukotoxin (ltx) and isoleukotoxin (iltx) Me esters, are metabolites of Me linoleic acid, an essential fatty acid. They have been assocd. with acute respiratory distress syndrome. The obsd. toxicity of ltx and iltx is, in fact, due to the metab. of the epoxides to their corresponding diols by sol. epoxide hydrolase (sEH). Herein, the authors demonstrate that ltx/iltx are toxic in a time-dependent manner to human sEH expressing cells with a LT50 of 10.6 .+-. 0.8 h and that ltx and iltx have KM of 6.15 .+-. 1.0 and 5.17 .+-. 0.56 .mu.M, resp., and Vmax of 2.67 .+-. 0.04 and 1.86 .+-. 0.06 .mu.mol/min/mg, resp., which can be inhibited by sEH inhibitors. The authors show that four major metabolites of ltx/iltx are formed in their system, including ltx/iltx free acid, ltxd/iltxd, free acid, and phosphotidylcholine and phosphotidylethanolamine contg. the carboxylic acid forms of both ltx/iltx and ltxd/iltxd, but that the only metabolite assocd. with toxicity is the carboxylic acid form of ltxd/iltxd, suggesting the involvement of cellular esterases. The authors demonstrate that a serine esterase inhibitor provides some protection from the toxicity of epoxy fatty esters to sEH expressing cells as do intercellular free sulfhydryls, but that this protection is not due to glutathione conjugation. With these data, the authors have proposed an extension of the metabolic pathway for ltx/iltx in eukaryotic cells. (c) 2000 Academic Press.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:186660 CAPLUS
DOCUMENT NUMBER: 133:70547
TITLE: Identification of CYP2C9 as a Human Liver Microsomal Linoleic Acid Epoxygenase
AUTHOR(S): Draper, Alison J.; Hammock, Bruce D.
CORPORATE SOURCE: Department of Chemistry, Bucknell University, Lewisburg, PA, 17837, USA
SOURCE: Archives of Biochemistry and Biophysics (2000), 376(1), 199-205
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leukotoxin (9,10-epoxy-12-octadecanoate) and isoleukotoxin (12,13-epoxy-9-octadecenoate) are monoepoxides of linoleic acid, synthesized by a cytochrome P 450 monooxygenase and possibly by an oxidative burst of inflammatory cells. Recent expts. in this lab. have indicated that the toxicity of leukotoxin and isoleukotoxin is not due to these epoxides, but to the 9,10- and 12,13-diol metabolites. Leukotoxin and isoleukotoxin are metabolized primarily by the sol. epoxide hydrolase to form ***leukotoxin*** ***diol*** . Investigations with recombinant cytochrome P 450 enzymes have demonstrated that leukotoxin and isoleukotoxin can be formed by these enzymes. This study used a combination of exptl. approaches to identify the major cytochrome P 450 enzyme in human liver involved in linoleic acid epoxidn. The kinetic paramenters were detd.; the Km of linoleic acid epoxidn. by pooled human liver microsomes was 170 .mu.M and the Vmax was 58 pmol/mg/min. Correlation anal. was performed using individual samples of human liver microsomes, and the best correlation of linoleic acid epoxidn. activity was with tolbutamide hydroxylase activity, CYP2C9. Recombinant CYP2C9 was the most active in linoleic acid epoxygenation, and antibody and chem. inhibition also indicated the importance of CYP2C9. This enzyme, therefore, may serve as a therapeutic target in the treatment of inflammation in order to reduce the amt. of circulating leukotoxin/isoleukotoxin and their related diols. (c) 2000 Academic Press.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:110452 CAPLUS
DOCUMENT NUMBER: 132:318802
TITLE: Leukotoxin and its diol induce neutrophil chemotaxis through signal transduction different from that of fMLP
AUTHOR(S): Totani, Y.; Saito, Y.; Ishizaki, T.; Sasaki, F.; Ameshima, S.; Miyamori, I.
CORPORATE SOURCE: Third Dept of Internal Medicine, Fukui Medical University, Fukui, 910-11, Japan
SOURCE: European Respiratory Journal (2000), 15(1), 75-79
CODEN: ERJOEI; ISSN: 0903-1936
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB When injected into animals, leukotoxin (Lx) causes acute lung injury which is assocd. with neutrophils infiltrating the lung tissues. However, the effect of Lx on neutrophils is still unknown, and recently it has been reported that Lx diol, a hydrolyzed metabolite, should be more potent than Lx in vitro. In this study, the authors examd. the effect of Lx and its diol on human neutrophils by assessing their chemotactic response, expression of adhesion mols., and prodn. of peroxides. Both Lx and its diol induced chemotaxis in human neutrophils via an involvement of pertussis toxin-sensitive G-proteins, but they did not influence the expression of adhesion mols. or the prodn. of peroxides. Furthermore, Lx synergistically affected chemotaxis with N-formyl-methionyl-leucyl-phenylalanine (fMLP), but not with endothelin 1. Neutrophil chemotaxis induced by both Lx and its diol was inhibited by phosphatidylinositol 3-kinase (PI3-K) inhibitors, but not by protein tyrosine kinase (PTK) inhibitors or by protein kinase C (PKC) inhibitors, whereas fMLP-induced chemotaxis was inhibited by PTK inhibitors, but not by PI3-K inhibitors or by PKC inhibitors. These results suggest that neutrophil chemotaxis induced by both Lx and its diol involves pathways different from those induced by fMLP. In conclusion, both leukotoxin and its diol metabolite induce chemotaxis in human neutrophils in an unique way and may act as important bioactive lipids when considering the pathol. mechanism of acute lung injury.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:394294 CAPLUS
DOCUMENT NUMBER: 131:168305
TITLE: Effects of linoleic acid metabolites on electrical activity in adult rat ventricular myocytes
AUTHOR(S): Stimers, Joseph R.; Dobretsov, Maxim; Hastings, Stephanie L.; Jude, Anthony R.; Grant, David F.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
SOURCE: Biochimica et Biophysica Acta (1999), 1438(3), 359-368
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leukotoxin (Lx), an epoxide deriv. of linoleic acid, has been suggested to be a toxic mediator of multiple organ failure in burn patients and of acute respiratory distress syndrome. Lx prodn. was recently shown during myocardial ischemia/reperfusion. However, a recent study suggested that to be toxic Lx must be metabolized to Lx-diol. In the present study, isolated adult rat ventricular myocytes were studied with the whole-cell patch-clamp technique to det. the effects of these compds. on cardiac elec. activity. Measurements of action potentials showed that neither linoleic acid nor Lx (100 .mu.M) caused any significant changes in action potential properties. However, Lx-diol in the range of 10-100 .mu.M produced a dose dependent increase in duration and a decrease in overshoot of the action potential. Subsequent voltage clamp expts. isolating Na current (INa) and transient outward K current (Ito) revealed that Lx-diol inhibited INa and Ito by about 80% at 100 .mu.M, while linoleic acid and Lx had no effect on these currents at the same concn. While Lx-diol produced the same inhibition of INa and Ito at 100 .mu.M, its effects were more potent on Ito with significant inhibition at 10 .mu.M. Lx-diol also hastened the activation kinetics of Ito but not INa. The action of Lx-diol was rapid (reaching steady state in 3-5 min) and was reversible in 5-10 min following washout. Thus, Lx-diol could favor arrhythmias or cardiac arrest in intact heart and may be responsible for the cardiac problems seen in systemic inflammatory response syndrome. These results further support the suggestion that Lx is not toxic in the heart but

rather must be metabolized to Lx-diol to produce toxic effects on cardiac muscle.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:365437 CAPLUS
DOCUMENT NUMBER: 129:36394
TITLE: In vitro biological effects of leukotoxin and leukotoxin diols on neutrophil
AUTHOR(S): Totani, Yoshitaka; Saito, Yuji; Sasaki, Fumihiko; Miyamori, Isamu; Ishizaki, Takeshi
CORPORATE SOURCE: Third Dep. Intern. Med., Fukui Med. Coll., Japan
SOURCE: Therapeutic Research (1998), 19(4), 1123-1126
CODEN: THREEL; ISSN: 0289-8020
PUBLISHER: Raifu Saiensu Shuppan K.K.
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Leukotoxin and leukotoxin diols increased neutrophil chemotaxis but did not affect the expression of adhesion mols. and peroxide prodn. by neutrophil.

L25 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:123974 CAPLUS
DOCUMENT NUMBER: 128:201056
TITLE: Methods of treating adult respiratory distress syndrome and other inflammatory diseases mediated by polyunsaturated lipid metabolites, and assays for epoxide hydrolase inhibitors
INVENTOR(S): Hammock, Bruce D.; Moghaddam, Mehran F.; Cheek, Jeffrey M.; Borhan, Babak; Fergusson, James; Grant, David F.; Greene, Jessica F.; Matoba, Kazu; Zheng, Jiang; Sisemore, Marlene F.
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9806261	A1	19980219	WO 1997-US14385	19970813
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5955496	A	19990921	US 1997-909523	19970812
AU 9740692	A1	19980306	AU 1997-40692	19970813
EP 926951	A1	19990707	EP 1997-938335	19970813
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6174695	B1	20010116	US 1999-312207	19990514

PRIORITY APPLN. INFO.: US 1996-23397P P 19960813
US 1997-909523 A 19970812
WO 1997-US14385 W 19970813

AB Methods are provided for treating inflammatory diseases mediated by polyunsatd. lipid metabolites by inhibiting epoxide hydrolase. The methods may be used for treating e.g. adult respiratory distress syndrome. Also provided are methods for assaying or screening the epoxide hydrolase inhibitors for inhibitory specificity and for toxicity, as well as novel biol. active THF diols of arachidonic acid, including antibodies thereto.

L25 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:621322 CAPLUS
DOCUMENT NUMBER: 127:230447
TITLE: Cytotoxicity of linoleic acid diols to renal proximal tubular cells
AUTHOR(S): Moran, Jeffery H.; Weise, Rick; Schnellmann, Rick G.; Freeman, J. P.; Grant, David F.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University

of Arkansas for Medical Sciences, Little Rock, AR, 72205-7199, USA
SOURCE: Toxicology and Applied Pharmacology (1997), 146(1), 53-59
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Monoepoxides of linoleic acid (leukotoxin and isoleukotoxin) have been assocd. with a variety of pathophysiol. diseases in humans including multiple organ failure. They also have been shown to be toxic when injected into exptl. animals. Because leukotoxin and isoleukotoxin are excellent substrates for epoxide hydrolases, the authors tested the hypothesis that the diol metabolites are less toxic than the parent monoepoxides using the rabbit renal proximal tubule (RPT) suspension model. An equimolar mixt. of the positional isomers of the Me esters of leukotoxin and isoleukotoxin did not cause cell death to RPT cells at concns. up to 1 mM using lactate dehydrogenase release as the endpoint. The corresponding diols, however, caused cell death in a time- and concn.-dependent manner beginning at 4 h and reaching 42% cell death in 6 h at 1 mM. Cell death was not due to oxidative stress since malondialdehyde content did not increase and the iron chelator deferoxamine and the antioxidant N,N'-diphenyl-1,4-phenylenediamine were not cytoprotective. In contrast, cell death was assocd. with mitochondrial dysfunction with respiration decreasing 54% prior to the onset of cell death. Secondary to the mitochondrial dysfunction, the diols completely inhibited active Na+ transport within 30 min of addn. These results suggest that the in vivo toxicity and pathophysiol. previously attributed to the monoepoxides of linoleic acid may be due to the diol metabolites.

L25 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:297665 CAPLUS
DOCUMENT NUMBER: 126:289133
TITLE: Bioactivation of leukotoxins to their toxic diols by epoxide hydrolase
AUTHOR(S): Moghaddam, Mehran F.; Grant, David F.; Cheek, Jeffrey M.; Greene, Jessica F.; Williamson, Kristin C.; Hammock, Bruce D.
CORPORATE SOURCE: Environ. Stud., DuPont Agric. Pro., Exp. Stn., Wilmington, DE, 19880-0402, USA
SOURCE: Nature Medicine (New York) (1997), 3(5), 562-566
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature Publishing Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leukotoxin is a linoleic acid oxide produced by leukocytes and has been assocd. with the multiple organ failure and adult respiratory distress syndrome seen in some severe burn patients. Leukotoxin has been reported to be toxic when injected into animals i.v. Herein, the authors report that this lipid is not directly cytotoxic in at least two in vitro systems. Using a baculovirus expression system the authors demonstrate that leukotoxin is only cytotoxic in the presence of epoxide hydrolases. In addn., it is the diol metabolite that proves toxic to pulmonary alveolar epithelial cells, suggesting a crit. role for the diol in leukotoxin-assocd. respiratory disease. In vivo data also support the toxicity of ***leukotoxin*** ***diol*** . For the first time the authors demonstrate that sol. epoxide hydrolase can bioactivate epoxides to diols that are apparently cytotoxic. Thus, leukotoxin should be regarded as a protoxin corresponding to the more toxic diol. This clearly has implications for designing new clin. interventions.

L25 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:161958 CAPLUS
TITLE: Study of the mechanism of inhibition of epoxide hydrolases by chalcone oxides.
AUTHOR(S): Morisseau, C.; Du, G.; Newman, J. W.; Nakagawa, Y.; Zheng, J.; Hammock, B. D.
CORPORATE SOURCE: Departments Entomology and Environmental Toxicology, University California, Davis, CA, 95616, USA
SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-126. American Chemical Society: Washington, D. C.
CODEN: 64AOAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Metab. of drugs and xenobiotics is among the important factors in detg. the biol. and toxicol. effects of exposure. Many mutagens and carcinogens are degraded by the sol. and microsomal epoxide hydrolases. Conversely, the diol resulting from the hydrolysis of leukotoxin by an epoxide hydrolase is the metabolite responsible for the toxicity of this compd. in cell culture. If prodn. of ***leukotoxin*** ***diol*** results in the clin. symptoms of ARDS, inhibition of the epoxide hydrolase could reduce symptoms. In this study, we report (1) the quant. anal. of the structure-activity relationship for about forty inhibitors (chalcone oxide derivs.) of sol. epoxide hydrolases, (2) the kinetic study of their action, and (3) the detn. of the structure of the enzyme-inhibitor complex. These results provide an understanding of the mechanism of inhibition permitting the design of therapeutic drug or pro-drug for the treatment of ARDS.

=> d his

(FILE 'HOME' ENTERED AT 14:16:02 ON 25 OCT 2002)

FILE 'CAPLUS' ENTERED AT 14:18:13 ON 25 OCT 2002
L1 81296 S ?HYPERTENS?
L2 3 S HAMMOCK B/AU
L3 2 S ZUREK G/AU
L4 18 S GEE S/AU
L5 69 S NEWMAN J/AU
L6 222 S ZHENG J/AU
L7 72 S (LINOLEIC ACID OR LEUKOTOXIN) (L)DIOL
L8 0 S L7 AND L1
L9 1 S L7 AND L2-L6
L10 0 S L1 AND L2-L6

FILE 'STNGUIDE' ENTERED AT 14:24:23 ON 25 OCT 2002

FILE 'CAPLUS' ENTERED AT 14:26:50 ON 25 OCT 2002

FILE 'STNGUIDE' ENTERED AT 14:26:50 ON 25 OCT 2002
L11 0 S L1 AND (L2 OR L3 OR L4 OR L5 OR L6)
L12 0 S EPOXIDE HYDROLASES
L13 0 S EPOXIDE
L14 0 S LINOLEIC ACID
L15 0 S LINO? (W) ACID?
L16 0 S GLUCURONIDE?

FILE 'CAPLUS' ENTERED AT 14:31:58 ON 25 OCT 2002
L17 0 S L11
L18 26879 S L14
L19 238 S L18 AND L1
L20 0 S L19 AND DIOL
L21 0 S L7 AND ?ECLAMPSIA?
L22 3 S ?ECLAMPSIA AND EPOXIDE
L23 0 S (EPOXIDE HYDROLASE) AND (LINOLEIC ACID DIOL)
L24 1 S LINOLEIC ACID DIOL
L25 13 S LEUKOTOXINDIOL OR LEUKOTOXIN DIOL
L26 0 S L25 AND (?HYPERTENS? OR ?ECLAMPS?)

=> log y

STN INTERNATIONAL LOGOFF AT 14:45:31 ON 25 OCT 2002